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Symmetry reversal in schizophrenia

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Abstract Schizophrenia is associated with cortical asymmetries concentrated in the left fronto-temporal hemisphere. In order to look for functional asymmetries between the two hemispheres, the stimulus–response times of patients were split into smaller periods and the interhemispheric and intrahemispheric correlations between these periods were investigated. Three groups were compared to each other: 22 patients with schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edn; DSM-IV) treated with neuroleptics; 24 psychiatric neuroleptic-treated patients without schizophrenia; and 30 healthy subjects. All subjects were investigated by simple (one stimulus–one response) and complex (two stimuli–two responses), auditory and visual, right-hemispheric and left-hemispheric stimulus–response tasks. There were no intrahemispheric but significant interhemispheric correlations between the two auditory and between the two visual time fragments in both the healthy and the neuroleptic control group. In contrast there was a significant intrahemispheric correlation between the auditory and visual time fragment in the left hemisphere of patients with schizophrenia and no interhemispheric correlation between the auditory times. The reduction of the interhemispheric auditory correlation is interpreted as an auditory disintegration, the appearance of the left-hemispheric audiovisual correlation as an audiovisual 'hyperintegration' in patients with schizophrenia. It is questionnable as to whether these findings are due to schizophrenia or to the neuroleptic treatment.

Key words bilateral asymmetry, interhemispheric correlation, neuroleptics, reaction times, schizophrenia, time fragments.

INTRODUCTION

The splitting up of stimulus–response times into small time fragments yielded significant interhemispheric correlations in a healthy group. Consequently, the question was whether this symmetry is conserved in patients with schizophrenia.

Gruzelier, as well as Lohr and Caligiuri, agreed that schizophrenia is associated with left hemisphere dysfunction.[1,2] Buchsbaum *et al*. and Falkai *et al*. supported this hypothesis by a vast body of evidence:[3,4] in schizophrenia the volume of the left hemisphere is reduced, especially that of the left prefrontal and temporal areas. The left lateral ventricle is enlarged. This asymmetry affects the structures of the brain as well as the functional parameters. A topographic asymmetry of P300 with reduced left temporal voltage was found by Salisbury *et al*.[5] Bustillo *et al*. reported an asymmetry of reaction times.[6] Russell *et al*. found that the left temporal lobe of individuals with schizophrenia is significantly hypoperfused compared to control measurements.[7] Maher *et al*. assumed that the deficit is due to a lack of normal asymmetry of lateralization in some schizophrenic patients.[8] Bodner *et al*. provided findings in the symmetry of frequency bands during task-related evidents.[9] Latour found an integer relationship between reaction time periodicities in motor responses of the eye to horizontal changes on the position of a fixation light and electroencephalogram (EEG)

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rhythms before and during the experiments.[10] There is a cycle time of 29 ms in rapid EEG rhythms, a time of 14.5 ms in left to right reaction times and 9.7 ms in right to left reaction times. Kristofferson found quantal steps in the threshold of duration discrimination after prolonged practice.[11,12]

For nearly a century the time structure of cortical processes was thought to be composed of small time units (von Baer[13] and Wundt[14]). We assumed the fragments of stimulus–response times to be integer multiples of such time units.

Singer and Gray assumed that the unity of an individual is represented by the synchrony of the underlying cortical activities.[15,16] The interhemispheric correlation of cortical areas contributes to this unity. A loss of interhemispheric symmetry could result in an incoherent, autonomous processing of the two hemispheres with a loss of cooperation and specialization between them.

The intrahemispheric and interhemispheric correlations between small periods of stimulus–response times were used to characterize the temporal structure of cortical processes and the changes in schizophrenia.

METHOD

The subjects of the present study were divided into three groups: mentally healthy subjects; patients with schizophrenia treated with neuroleptics; and neuroleptic-treated patients without schizophrenia. The auditory and visual stimulus–response times were measured and split into small periods and the correlations between these periods were then calculated and interpreted.

The first group consisted of 30 mentally healthy test persons (21 male, nine female). Their mean age was 28.3 ± 5.9 years (range: 22–68 years). They were not on any medication except ovulation inhibitors in some cases.

The second group consisted of 22 patients with schizophrenia diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th edn; DSM-IV; 16 male and six female). All had post-remissive symptoms such as deficiencies of emotion and concentration and were treated with antipsychotic medication (dopamine antagonists or serotonin–dopamine antagonists). They were between 18 and 44 years old (mean age: 32.6 ± 10.5 years).

The third group consisted of 24 psychiatric patients without any symptoms of schizophrenia who were treated with neuroleptics. There were 13 male patients and 11 female patients with a mean age of 41.8 ± 15.7 years (range: 17–81 years). They suffered from depression, personality disorders and other non-psychotic DSM-IV disorders. All of them were treated with low-potency neuroleptics except three patients who received high-potency neuroleptics.

Subjects with any musculoskeletal complaints or vision/hearing problems that might interfere with the measurement of the reaction time were excluded.

The present study was approved by the local ethics committee at the University of Erlangen-Nuremberg. Informed consent was obtained according to the Declaration of Helsinki.

Every subject had to pass four auditory and four visual stimulus–response tasks. The test was designed to be monohemispheric. Before starting the subject received instructions from the supervisor and had the possibility to exercise the tasks a few times. Only the hand that was needed for the test was allowed to be on the keyboard. The keys had to be pressed as fast and as accurately as possible when the stimulus appeared.

For the visual stimulus–response task the subjects faced a laptop screen located approximately 40 cm in front of their eyes and placed their fingers on the corresponding keys of the keyboard. The stimulus was a vertical line of five 'O's appearing below one of the permanent numbers '1' or '2'. If the stimulus appeard below the number '1', the subject had to press the 'j' key, if was is below the number '2', the subject had to press the 'k' key. The left-handed tasks were performed analogously with the 'f' key corresponding to the '1' and the 'd' key to the '2'.

There was an arrow in the middle of the screen that had to be fixed during the task, therefore only one half of the visual field was involved. The responding hand was on the same side as the stimulus so that mainly the contralateral hemisphere performed the task. The display used for the stimuli was 10 cm × 5 cm in size.

For the auditory stimulus–response task the subjects used earphones. The auditory stimulus was either a high or a low frequency tone given to only one ear. The responding hand lay on the side of the tone so that mainly the contralateral hemisphere performed the task. The high frequency tone in the right ear was answered by pressing the 'j' key, the low frequency tone by pressing the 'k' key. The left-sided conditions were symmetrical: in response to the high frequency tone the 'f' key was hit and in response to the low frequency tone the 'd' key was hit.

In the simple version of the stimulus–response time, only one stimulus was presented successively 100 hundred times; in the complex version one of two possible stimuli was presented and answered by pressing the corresponding response key (as aforementioned). The tasks took approximately 1.5 h with 600 visual and 600 auditory stimuli. The random interstimulus interval was 2500 ms on average to prevent guessing. All

subjects were tested twice within 2 weeks. All response times were not measured simultaneously but successively.

The four fragments of the stimulus–response times (Tar, Tal, Tvr and Tvl (T, small period of the response time; a, auditory; v, visual; r, right hand; l, left hand)) were calculated by a computer program described by Kalb.[17]

The two-sided Mann–Whitney *U*-test and the Wilcoxon test were used for single comparisons between the four times of the first session and between the corresponding times of the second session. The significance level was set at $P \leq 0.05$. We analyzed the mean values, the median values and the standard deviations of the time fragments. The correlations between the different times were quantified by the Pearson correlation coefficient used to compute the correlation between Tar and Tal, Tvr and Tvl, Tar and Tvr and Tal and Tvl.

RESULTS

The patients with schizophrenia differed from the healthy and the neuroleptics control group. Whereas the healthy and the neuroleptics control group showed significant interhemispheric but no intrahemispheric correlations, there was a reversal in the schizophrenic group. Here there was a significant left-hemispheric audiovisual correlation and a reduced auditory–auditory correlation.

Four different periods of stimulus–response times were investigated: Tar, Tal, Tvr and Tvl.

The mean values of the healthy control group ($n = 30$) were: Tar = 14.6 ± 2 ms, Tal = 14.5 ± 1.8 ms, Tvr = 14.7 ± 1.9 ms and Tvl = 15.4 ± 2.0 ms.

The mean values in the schizophrenic group ($n = 22$) were: Tar = 14.8 ms ± 2.2 ms, Tal = 14.9 ± 3.0 ms, Tvr = 16.1 ± 2.9 ms, and Tvl = 16.2 ± 3.9 ms. The visual mean values were slightly higher than in healthy subjects. The doses of the neuroleptic medication and the chlorpromazine equivalent doses are shown in Table 1.

The mean values in the neuroleptic control group ($n = 24$) were: Tar = 14.8 ± 1.6 ms, Tal = 15.2 ± 1.9 ms, Tvr = 14.5 ± 2.2 ms, and Tvl = 14.7 ± 2.0 ms. The diagnoses and the neuroleptic medication of this group are shown in Table 2.

The 30 healthy subjects had a significant correlation between the two auditory times Tar and Tal (Fig. 1a). The Pearson correlation coefficient was r = 0.773 ($P < 0.01$). The two visual periods Tvr and Tvl showed also a significant correlation but a lower Pearson correlation coefficient: r = 0.578 ($P < 0.01$). There were no significant audiovisual correlations in the healthy group: the correlation coefficient of Tar and Tvr was r = 0.155 ($P = 0.414$, NS), the correlation coefficient of Tal and Tvl was r = 0.225 ($P = 0.231$, NS; Fig. 1b). This means that the auditory and visual times were completely independent from each other. Approximately half of the healthy subjects had Tay > Tvy and the other half had Tay < Tvy (where y = r or l).

Table 1. Neuroleptic equivalent dose in the patients with schizophrenia

Code	Neuroleptics	Chlorpromazine equivalent dose (mg)
S01	Benperidole	2400
S02	Risperidone Flupentixol Amisulpirid	670–1000
S03	Haloperidol	160–240
S04	Risperidone	200
S05	Clozapine	250–750
S06	Risperidone	100
S07	Perazine	50
S08	Risperidone Haloperidol	800–1100
S09	Amisulpirid	520–700
S10	Clozapine	550–1650
S11	Risperidone Promethazine	212–250
S12	Thioridazine	40
S13	Olanzapine	80–200
S14	Clozapine	600–1800
S15	Olanzapine	120–300
S16	Risperidone	200
S17	Pipamperone	20
S18	Olanzapine	120–300
S19	Sulpirid	120–200
S20	Olanzapine Pipamperone	100–220
S21	Risperidone Olanzapine	180–300
S22	Sertindole	128–320

The patients with schizophrenia treated with high-potency neuroleptics had no significant interhemispheric correlation in the auditory time fragments (Fig. 1c). The correlation coefficient of Tar and Tal was r = 0.354 ($P = 0.106$, NS). However, the two visual times retained a significant correlation. The correlation coefficient between Tvr and Tvl was r = 0.571 ($P < 0.01$). Interestingly, the patients with schizophrenia had a significant audiovisual correlation in the right-handed tasks but not in the left-handed ones. The correlation coefficient of Tar and Tvr was r = 0.574 ($P < 0.01$) but the correlation coefficient between Tal and Tvl was r = 0.038 ($P = 0.05$, NS; Fig. 1d and 2). The auditory left–right difference in patients with schizophrenia did not correlate significantly with the neuroleptic dose of

Table 2. DSM-IV diagnoses and neuroleptic equivalent doses (chlorpromazine) of neuroleptic-treated patients without schizophrenia

Subject	Diagnoses	Chlorpromazine equivalent dose (mg)
027	296.40	150
028	296.22	40
029	294.9	20
030	296.22f	25
050	296.23	50
053	293.83	20
054	300.4	10–20
056	290.13	20
069	304.80	20
071	293.83	200–300
090	304.80	40–80
112	301.82	20–50
114	300.00	12,5
125	304.80	90–150
129	295.70	25
138	296.80	20
139	301.82	50
140	303.90	50
141	293.83	75
143	311.00	50
146	301.83	40
187	296.22	30
192	296.21	10
200	296.04	550–850
204	296.22	30–50
205	309.4	440–700
208	296.32	100–300
210	296.22	40
222	293.89	30–50
226	303.90	80–200
243	296.53	200–500
251	296.22	62,5

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn.

these patients ($r = 0.222$, $P = 0.321$). There was no significant difference between the two mean auditory or the two visual times in this group.

In order to exclude the possibility that these findings in schizophrenia are caused by the neuroleptic treatment, a second control group of neuroleptic-treated patients without schizophrenia was tested. These patients had a significant correlation between the two auditory times and between the two visual times, just as the healthy subjects (Fig. 1e). The correlation coefficient between Tar and Tal was 0.781 ($P < 0.01$), that between Tvr and Tvl was 0.785 ($P < 0.01$). There were no significant audiovisual correlations in this group (Fig. 1f). The correlation coefficient of Tar and Tvr was r = –0.068 ($P = 0.753$, NS). Here too, the auditory and visual times were independent of each other.

Summing up, there was a reversal of symmetry in patients with schizophrenia in contrast to healthy subjects and neuroleptic-treated patients without schizophrenia. It is intriguing that only those correlations were changed when the auditory, right-hand time Tar was involved. The correlations between Tar and Tal and between Tar and Tvr distinguished the patients with schizophrenia from the two control groups. Nearly all subjects and patients in all groups were right-handed.

DISCUSSION

The laterality of reaction times and other neurophysiolgical findings in patients with schizophrenia has been established for a long time. The present study showed additionally that the laterality is extended to the time periods of stimulus–response tasks, that healthy subjects and neuroleptic-treated patients without schizophrenia do not show this laterality, and that unilateral audiovisual temporal relations are changed also.

The study of Fishman *et al*. found a slowing in auditory right-hand tasks.[18] This could not be confirmed in the present study. Here, the absolute distance between the two auditory times was increased but no auditory time showed a clear increase compared with the contralateral one. There are other studies dealing with auditory reaction tasks that did not find any side difference either. Malathi *et al*., for example, found no significant difference in auditory reaction times within a schizophrenia group when the stimulus was presented to the right ear or left ear ($P > 0.05$).[19]

Posner *et al*. found a lateralized abnormality in visual reaction tasks: longer reaction times to uncued targets in the right visual field than in the left visual field.[20] Wigal *et al*. observed this lateralized abnormality in reaction time only in a drug-free group of schizophrenic subjects, but not in a group of drug-treated schizophrenic subjects.[21] Bustillo *et al*. investigated cued visual reaction times in non-deficit and deficit patients with schizophrenia.[22] The non-deficit patients exhibited a significant and abnormal asymmetry, with a slower reaction time to targets presented in the right visual field than in the left visual field. This right visual field disadvantage was found with both versions of the task, but only at the 100-ms cue–target interval. The deficit patients were slowest in overall reaction time but, similar to the normal subjects, showed no asymmetry.

Mandal *et al*. found a bilateral motor transfer deficit in schizophrenia.[23] Schizophrenic subjects compared with normal subjects showed a poor bilateral transfer of skill in terms of errors committed. However, the

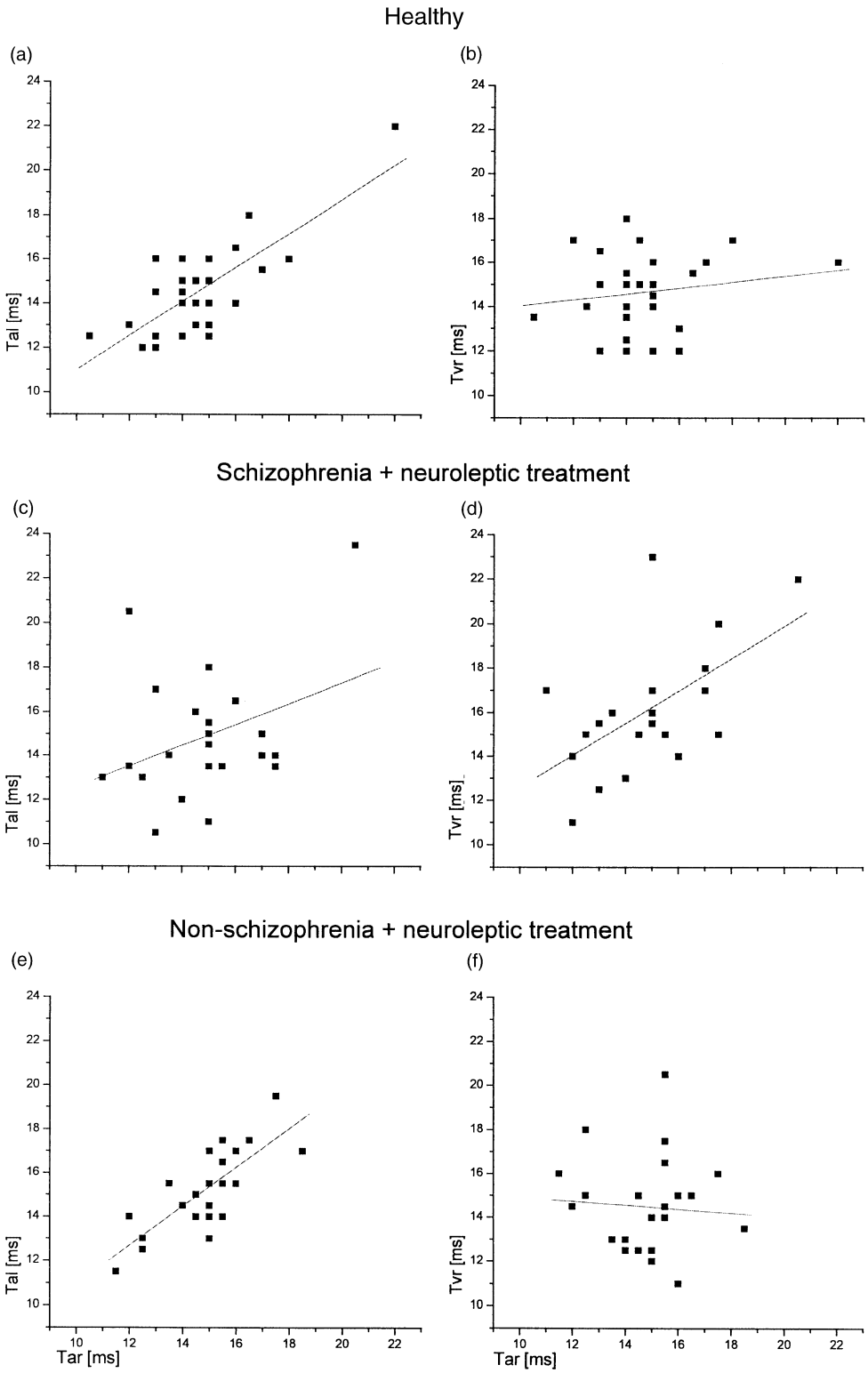

Figure 1. Correlations between the four different time fragments: Tar, time fragment, auditory, right hand; Tal, time fragment, auditory, left hand; Tvr, time fragment, visual, right hand; Tvl, time fragment, visual, left hand. (a) Correlation between Tar and Tal in healthy subjects. (b) Correlation between Tar and Tvr in healthy subjects. (c) Correlation between Tar and Tal in patients with schizophrenia. (d) Correlation between Tar and Tvr in patients with schizophrenia. (e) Correlation between Tar and Tal in neuroleptic-treated patients without schizophrenia. (f) Correlation between Tar and Tvr in neuroleptic-treated patients without schizophrenia.

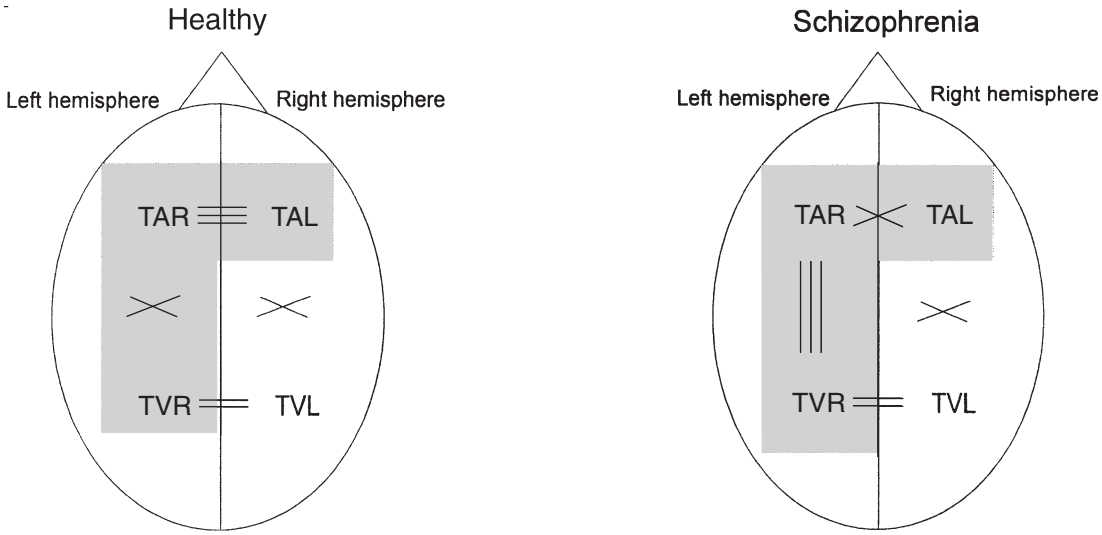

Figure 2. Overview of the correlations between the four time fragments in healthy subjects and patients with schizophrenia; parallel lines: correlation; crossing: no correlation.

group difference was non-significant in terms of response time.

There are many reports about a left temporal deficit of P300 in patients with schizophrenia (e.g. Ford *et al.*[24]). Endrass *et al.* interpreted their event-related potential (ERP) findings as a deficit in schizophrenia to transfer verbal information from the right to the left hemisphere via the corpus callosum.[25]

Electroencephalogram coherences have been an important tool to investigate the laterality of brain functions. Gomez and Lopera suggested that disengaged (non-connected) cortical graphs produced 'fuctional disconnection syndromes', which could cause some symptoms in schizophrenia.[26] Wada *et al.* found a significantly higher intrahemispheric coherence of the resting EEG for the delta band from resting to photic stimulation-related reactivity in schizophrenic patients compared to control subjects.[27] These findings provided evidence that schizophrenic patients have abnormal EEG coherence in both resting and stimulus conditions. Mann *et al.* found significantly higher intrahemispheric coherences in schizophrenic patients and in their siblings.[28] They considered that increased coherence might be a vulnerability marker for schizophrenia. Winterer *et al.* found that spectral coherences (0.5–5 Hz) were reduced in the temporal lobes of schizophrenics and their unaffected siblings.[29] These findings were most pronounced for the interhemispheric coherence linking both posterior temporal lobe areas and were seen as a potentially heritable trait related to genetic risk. Norman *et al.* proved frontal–temporal connectivity in schizophrenia and considered a disruption as having a specific relationship to reality distortion symptoms.[30]

The interpretation of our findings used the fact that the right-handed tasks correspond to the left hemisphere and the left-handed tasks to the right hemisphere. Thus, the significant correlations between the time periods of stimulus–response tasks could be interpreted as temporal correlations between the corresponding brain areas. Because the tasks were performed one after the other, the symmetries are equivalent to temporal invariants. The correspondence between the tasks and the brain areas is justified by anatomy and the findings that confirm the dominant role of the left fronto-temporal hemisphere in the pathogenesis of schizophrenia. Relating the findings of the present study to the brain, there were no significant intrahemispheric correlations but significant interhemispheric correlations between the two auditory and between the two visual times in the healthy and the neuroleptic control group. In contrast, there was a significant intrahemispheric correlation between the auditory and visual times of the left hemisphere in patients with schizophrenia but no significant interhemispheric correlation between the two auditory times.

The reduction of the interhemispheric auditory correlation in patients with schizophrenia is interpreted as an interhemispheric auditory disintegration, the appearance of a left-hemispheric audiovisual correlation as a left-hemispheric audiovisual 'hyperintegration'. The fact that neuroleptic-treated patients without schizophrenia did not show these findings is interpreted as their being not caused by the neuroleptic treatment.

In healthy subjects the interhemispheric correlation between the auditory and between the visual times is

interpreted as the precondition for an integration into one uniform experience (the brain could represent the identy of modality in both hemispheres by an identity of times). The non-correlation between the auditory and visual times in healthy subjects is interpreted as a separation between auditory and visual experiences (the brain could represent the modality difference between auditory and visual experiences by that time difference).

The interpretation of the intrahemispheric correlation between the auditory and the visual times of the left hemisphere may help to understand the origin of some schizophrenic symptoms. If the distance between the two modalities in the left hemisphere is reduced, this could cause audiovisual experiences such as perceptual delusions. The non-correlation between the two auditory times could cause auditory hallucinations because they cannot be fused into one auditory experience.

To make sure that these findings in patients with schizophrenia were not caused by neuroleptics a second control group consisting of non-schizophrenic patients treated with neuroleptics was investigated. These patients produced the same results as the healthy group. This is an argument against the possibility that the symmetry reversal in patients with schizophrenia is produced by neuroleptics. Yet, the neuroleptics control group was mostly treated with low-potency neuroleptics whereas all patients with schizophrenia were treated with high-potency neuroleptics.

These findings are valid only for statistical groups, not for individuals. Two healthy subjects produced results similar to the schizophrenic group and seven patients with schizophrenia displayed values similar to the healthy group. The two healthy subjects exhibited a reversal of symmetry without having any schizophrenic symptoms. This means that the reversal of symmetry is not sufficient to cause the symptoms of schizophrenia. The seven patients with schizophrenia treated with high-potency neuroleptics had a normal symmetry and no positive symptoms. Either the symmetry in these patients improved with neuroleptics or the reversal of symmetry is not necessary for the symptoms. The other schizophrenia patients treated with high-potency neuroleptics had a reversed symmetry and no positive symptoms. The non-schizophrenic control group treated with low-potency neuroleptics had a slightly higher symmetry than the healthy group. The question is whether this is an effect of the neuroleptic drugs. These results show that there must be an additional factor such as an increased function of the dopaminergic system[31–35] in order to produce the positive symptoms. The causes of the asymmetry should be investigated. Perhaps the asymmetry of auditory elementary times is compatible with the 'transcallosal misconnection syndrome'.[36]

The present study provided empiric evidence that small periods of stimulus–response times show significant interhemispheric correlations but no significant intrahemispheric correlations in a healthy control and a non-schizophrenic control group treated with neuroleptics. In patients with schizophrenia there was a reversal of symmetry: the interhemispheric correlation between the two auditory times vanished and an intrahemispheric audiovisual correlation in the left hemisphere emerged. This has been interpreted as an auditory disintegration and a left-hemispheric audiovisual hyperintegration in patients with schizophrenia.

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